DISEASES IN SEARCH OF VIRUSES

BY

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Everyone agrees that tremendous changes have occurred in the past few years in the field of the infectious diseases. Formidable weapons have been forged both for the treatment and the prevention of bacterial infections. As a result, diphtheria has become almost extinct and the enteric diseases are much reduced, patients with streptococcal disease and with pneumonia less often require hospital treatment, and the burden of acute illness in childhood has considerably lightened. Virus infections have not, however, altered in the same way or to the same extent. Some, such as poliomyelitis, have become a threat to both children and adults. Previously undescribed conditions such as myalgic encephalomyelitis or Royal Free disease, aseptic meningitis with an exanthem and little known syndromes such as herpangina, pharyngo-conjunctival fever and Bornholm disease have achieved a position of interest and even of importance as causes of morbidity. Moreover, the development of new techniques for the cultivation of viruses has led to the realization of a method of control of certain diseases and to a new look in regard to diagnosis. These changes have affected the work of both clinicians and microbiologists, and yet there has also arisen a considerable divergence of outlook between these two groups of medical men. One could almost say that they live in two different worlds.

The virologist, being equipped with new techniques for the laboratory study of viruses, has been more and more excited over the possibility of fundamental discovery concerning the nature of viruses, of their mode of multiplication and of the possibility of restraining their multiplication by chemical substances. Whenever he has occupied his time with human specimens he has found less difficulty in recovering viruses than in classifying the agents thus recovered and in relating their presence in specimens to the particular phase of illness or health existing in those from whom they were derived. There has therefore arisen the phrase of "Viruses in search of disease" which has been applied chiefly to the poliomyelitis-like viruses, to the Coxsackie viruses and to the adenoviruses. One gets the impression that virologists are at times unmoved by the clinical implications of their discoveries and that therefore they are sometimes tempted to urge the use of prophylactic weapons against viruses before it has even become apparent that they are a significant cause of human distress!

The clinician's world is of course familiar to most of you. He moves in an atmosphere of individual illnesses or of family outbreaks where diagnosis and treatment are the paramount needs. He looks on viruses as mysterious microbes very similar to bacteria except in size and blames all diseases of unknown aetiology upon their activity. He is impatient to solve clinical problems in the way that so many problems were solved in the past, namely by first delineating a syndrome sufficiently clearly for it to be called a clinical entity and then by seeking investigation from all possible angles in order to uncover the virus lurking in the patients' interior. Unfortunately clinicians do not always understand the importance of epidemiological studies, the meaning of latent or subclinical forms of virus infection and the significance of virus infections in relation to human ecology (in spite of the prevailing influence of rabbit myxomatosis!) Naturally as a clinician I am sympathetic to the clinician's difficulties, and I am equally conscious of the dangerous path which virology is tempted to pursue. I therefore feel it my duty to try to bring together these two contrasting points of view whenever I

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can. To do this I must attempt to make the virologist's world a little more easy for clinicians to understand.

Virus Growth in Tissue Cultures

Research on animal viruses has characteristically depended upon the introduction of methods of cultivation, each one of which has yielded a certain harvest of knowledge but which has eventually failed to throw fresh light on existing problems. The new look in virus research at the present time stems from the introduction of tissue culture methods by the Boston group of workers centring around Enders at the Boston children's hospital. Helped by the use of antibiotics to control contamination, Enders transformed tissue cultures from their previous position of technical complexity to a method capable of exploration by any laboratory. He was also instrumental in placing the tissue cultures within reach of the low power of a microscope so that simple histological observation of the changes wrought by virus multiplication could be effected.

The two chief ways of preparing tissue cultures for virus cultivation are the explant method where morsels of tissue are embedded in a plasma clot and allowed to develop a halo of growing cells and the roller-tube technique of cells dispersed by trypsinization where the wall of the test-tube becomes covered with a sheet of cells. Virus growth in cells may produce disintegration and cell-death as with poliovirus or else the cells may alter morphologically but remain alive as with the adenoviruses. In both cases the changes observed microscopically are termed cytopathogenic alterations but it is occasionally true that viruses may grow in cells without producing any visible alterations. Cytopathogenic changes form the basis of methods for the titration of virus and of neutralization tests for measuring specific antibodies against the viruses in human or animal sera.

Morphological studies of viruses show a great variation but animal and human viruses are usually composed of small rounded particles as viewed by the electron-microscope. Internal complexity of organization of these elementary bodies is sometimes revealed by methods such as exposure of the virus to enzyme action. Similar internal complexity is revealed by the thin tissue-slice method of electro-micrography perfected by Councilman Morgan and his colleagues in New York. The virus bodies of vaccinia and herpes are readily seen by this method developing in cytoplasmic granular areas within complete or incomplete shells of a surrounding membrane; but in the case of influenza no organized structure is found except at the cell surface. Here the rounded bodies and filamentous forms can be seen escaping from the cytoplasm in great numbers. The development of the virus from the moment of entry into the cell until its release is hidden from view and cannot for some hours be followed even by chemical or serological methods. It seems that the virus particle merges its identity with the cell nucleus or cytoplasm and diverts metabolic activity towards the replication of its own genetic material which resides in its nucleic acid content. Thus the multiplication of viruses is so different from that of bacteria that we are justified in regarding them as a distinct order of organized life, if indeed one can regard them as possessing the essential attributes of living matter.

SOME COMMON INFECTIONS AND THEIR VIRUSES

Now let us turn to the diseases which either have been in search of viruses until recently or which still are in search of their causative organisms. First let us consider the exanthemata—measles, rubella, chickenpox and herpes zoster:

The Exanthemata

Measles virus was transmitted to monkeys some years ago but no one was really convinced that a successful method of laboratory culture had been found until the Boston workers published their study on measles virus in tissue culture. The virus produces an unusual cytological change—the various cells of a human or monkey cell

culture merge their identity into a syncytium so that large giant cells are produced. One might in passing mention that giant cells can readily be demonstrated by swabbing the nares or nasopharynx in children with measles and smearing the cellular exudate on slides: this is a useful diagnostic method for measles. But the tissue culture giant cells have permitted the development of work on antibodies during convalescence from infection and the titration of gamma globulin against measles virus. Moreover, Enders has carried the virus in cultures of human amnion, transferred it to chick embryo cultures and is approaching the development of a vaccine against the disease. A more doubtful line of work is the present suggestion that measles is related to dog distemper virus. This arose from the demonstration that most children develop antibodies to distemper virus as they grow up. But the distemper virus produces such distinctive changes in the ferret that it seems to be unlikely that this virus is related to measles and more work on this theme is required. Rubella has so far defied attempts to define its causation. Chickenpox and herpes zoster virus have been grown in tissue cultures but transfer from one culture to the next can only be made by using intact cells, i.e. by grafting. Grinding up the cells prevents the virus from re-entry into new cells so that the relation between virus and host cell must be extremely intimate. Glandular fever has proved much more baffling. No success has been achieved in growing the agent associated with mononucleosis accompanied by a positive Paul Bunnell reaction. Yet a few cases of apparent glandular fever with a negative Paul Bunnell test have yielded Toxoplasma on cultivation. This organism is not of course a virus but the proof that it can cause mononucleosis shows that glandular fever is a syndrome rather than a disease.

Alimentary Diseases

Next the alimentary viruses require consideration. The innocent term "D. and V." obviously includes many unrelated conditions. I personally agree with the suggestion that various coliform bacteria are important causes of infantile gastro-enteritis perhaps especially the form occurring as outbreaks in maternity homes and hospitals. Attempts to demonstrate viruses which cause gastro-enteritis have not been successful, though Gordon in the U.S.A. has transmitted diarrhoea with cell-free filtrates of stools to human volunteers. But none of the welter of viruses found in the stools of healthy and sick children has yet been shown clearly to bear an aetiological relation to gastro-enteritis. Nor has the virus of hepatitis or of homologous serum jaundice been cultivated successfully though again the human volunteer has conclusively proved that both viruses exist in human specimens or excreta. Here then is a big group of alimentary diseases in search of viruses.

THE ENTERO-VIRUSES (*Orphan and Coxsackie viruses*)

If we pass from consideration of the alimentary diseases to the viruses which inhabit the alimentary tract, the present situation concerning the poliomyelitis-like viruses and the Coxsackie group of viruses forms another problem, this time of viruses in search of disease.

A large family of viruses is now known which consists of many different antigenic species and which have hitherto been grouped either as "orphan" viruses or as belonging to the Coxsackie viruses.

Coxsackie Viruses

The Coxsackie viruses were recovered first of all and were found by Dalldorf by using a method of inoculation of human specimens into suckling mice. The first strains were recovered from the stools of children ill during an outbreak of poliomyelitis in the little town of Coxsackie in the New York State. The viruses would not grow in adult mice or infect monkeys and it was hard to associate them with specific clinical illnesses. Since then a large number of similar viruses with the same inability to attack adult mice yet with pathogenic properties in baby mice has been recovered. Some,

now known as Coxsackie A viruses, cause necrosis of striated muscle with resulting flaccid paralysis of the mice, and others (Coxsackie B) cause encephalitis in baby mice but no muscle lesions. Twenty or more serologically different types of Coxsackie A viruses and six variant B viruses have been delineated.

The clinical disease now accepted as being due to Coxsackie A viruses is a trivial fever of infants and children associated with herpes-like vesicles on the palate. This is herpangina as described by Zahorsky in 1920 and it has been found as family outbreaks or larger epidemics in the summer season. Yet a majority of children from whom the Coxsackie A viruses have been recovered have remained clinically well so that infection is inapparent or subclinical. Dalldorf felt that poliovirus infection might in some way be potentiated by Coxsackie virus but could not prove this except that he found both viruses to be present in some faeces. The Coxsackie B viruses are biologically quite distinct. They are accepted as a cause of Bornholm disease and also as a cause of infantile myocarditis. In addition they have been found in faeces or the C.S.F. of some cases of lymphocytic meningitis.

Echo Viruses

It is usually difficult to cultivate the Coxsackie viruses in tissue cultures though this has been done with some strains. So when viruses were recovered from tissue cultures inoculated with stools and which would neither infect baby mice nor monkeys, it was realized that yet another group of enteric viruses existed which belonged neither to the polio nor to the Coxsackie group. As no one could associate these viruses with any clinical syndrome they were termed "orphans" or to give them their full title—the ECHO (enteric, cytopathogenic, human orphan), viruses. If one were to call the Coxsackie viruses the first cousins of polio, one ought to call the ECHO strains poliovirus second cousins. Already sixteen serologically different types are known.

The Lymphocytic Meningitis Syndrome

Wallgren in 1924 drew attention to lymphocytic meningitis as an important syndrome of multiple aetiology and called the non-bacterial forms "aseptic meningitis". With increased study of outbreaks of poliomyelitis many cases of non-paralytic disease have been recognized whose clinical picture conforms to Wallgren's description. However, when an aetiological study of lymphocytic meningitis is attempted, it has been the experience of many workers that the polioviruses will only account for a third or less of all the cases. Some few are due to mumps (with or without parotitis), and fewer still to lymphocytic choriomeningitis virus derived probably from house-mice. In Sheffield Drs. Tyrrell, Clarke and Heath have studied an outbreak of lymphocytic meningitis which appears to have been due to a single species of enterovirus. The epidemic was part of a general European conflagration of which the first signs appeared in 1955 in the Marche province of Italy.

From the throat and also from the stools of the patients an Italian virologist called Archetti readily recovered strains of a virus which he regarded as a Coxsackie A virus. The epidemic was not reported at the time. In 1956, first in East Anglia, then in Belgium, the Netherlands and many parts of Germany and then in the Midlands of England, aseptic meningitis occurred as an epidemic, chiefly affecting children but now accompanied by a definite rash in about one fifth of the cases. The rash is a blotchy or morbilliform eruption resembling roseola infantum. In Sheffield, Dr. Heath had been working with a modified strain of poliovirus type 2 in tissue culture and had learnt the appearances of a feebly virulent strain in monkey kidney cells. When throat swabs and stools from this "rash disease" were inoculated into kidney cell cultures, somewhat similar appearances were seen, suggesting feeble virus activity. Many strains of a virus were readily cultivated but for some time these could not be identified. Then one day some baby mice were inoculated with the tissue cultures and much to our surprise the typical appearances of a Coxsackie A virus were obtained. Yet direct inoculation of stools or throat swabs into mice failed to produce any illness. The viruses

were next compared with others received from the East Anglian and other European outbreaks and found to be serologically identical. Ultimately they were proved to be examples of a virus hitherto called an ECHO type 9, of which the prototype strain was recovered from the stool of a healthy child in Cincinatti. It thus seems that the ECHO 9 is really a Coxsackie A virus and is one cause of lymphocytic meningitis.

Meanwhile the story of aseptic meningitis has not ended with this ECHO 9 experience. ECHO viruses types 4 and 6 have also caused outbreaks of aseptic meningitis. Yet we still encounter cases from whom no viruses can be recovered either from stools or C.S.F. The problem of lymphocytic meningitis is thus still a task for the future which is made worse by the multiplicity of the virus species concerned in its aetiology. The enteroviruses like the Salmonellae seem perfectly adapted as human parasites and they furnish a vast and perhaps a growing challenge. For just as poliomyelitis has become an epidemic disease largely because of the postponement of the initial infection with poliovirus from infancy to a later age, so the enteroviruses may cause clinical disease if they first encounter the child after the period of infancy has passed.

RESPIRATORY DISEASES IN SEARCH OF VIRUSES

The number of known viruses which can cause respiratory disease is growing and yet a large proportion of the total of acute respiratory disease remains of undetermined aetiology. The four basic syndromes of influenza, the common cold, atypical pneumonia and acute undifferentiated respiratory disease still furnish a reasonably complete description of the clinical counterparts of the various non-bacterial respiratory diseases. These clinical syndromes are depicted on the left in the diagram and the known aetiological entities on the right (*Figure* 1).

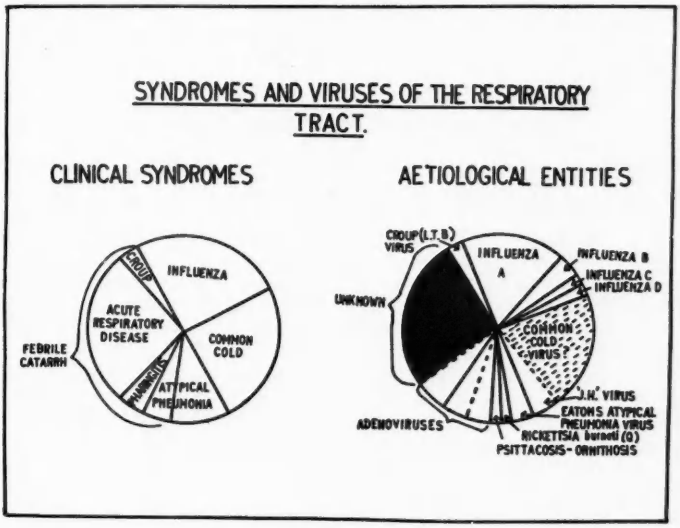

Figure 1

Influenza

Influenza is largely accounted for by infection with the two groups of influenza viruses A and B. Influenza C has not so far occurred in epidemic fashion but appears to be a cause of sporadic febrile respiratory illness. Influenza D is the name given to a virus recovered originally in Japan from cases of pneumonitis in the neonatal period. Until last year it had only been found to be associated with sporadic illness but an epidemic occurred in Vladivostok in 1956 and this was apparently regarded as clinical

influenza. The D virus differs a good deal from the other influenza viruses because of its destructive effect on cells in tissue culture and by reason of its recovery from wild mice. Nevertheless, it produces agglutination of red cells and has other qualities justifying inclusion in the group of viruses known as "myxovirus" which includes influenza, mumps and Newcastle disease virus of fowls.

Croup

A newly recovered haemagglutinating virus also with antigenic relationship to mumps virus is that recovered from cases of acute obstructive laryngo-tracheo-bronchitis (Croup) in 1956 simultaneously by Chanock in the U.S.A. and Beale in Toronto. Dr. Clarke is working with the L.T.B. virus in Sheffield and is endeavouring to find out whether cases of acute respiratory disease in adults are due to this virus or whether it is only a cause of illness in babies.

Atypical Pneumonia

Numerous viruses are associated with the atypical pneumonia syndrome, but that form of the disease in which serum agglutinins develop that are active against red cells in the cold (cold agglutinin antibody) has until recently been regarded as of unknown origin. Now, however, fresh evidence has been obtained by Boston workers, associating the disease with the virus recovered by Eaton during the war. One still feels that atypical pneumonia is not a numerically common form of acute disease of the respiratory tract.

Febrile Catarrh and Adenoviruses

The name "febrile catarrh" was originally used by Drs. Andrewes, Smith and myself in 1938 for cases of febrile respiratory disease encountered in epidemics amongst servicemen and particularly in recruits, which were not due to the influenza A virus. It was admitted that the name covered a heterogeneous collection of cases including some with pharyngitis and others with exudate on the tonsils as well as those with an influenza-like symptomatology. No progress was made towards a solution of the aetiology of febrile catarrh until the recovery of the adenoviruses (originally termed the APC or adenoidal-pharyngeal-conjunctival viruses) in the U.S.A. in 1953. The earliest work with the adenoviruses by Rowe, Huebner and others in Washington showed that certain serological types were commonly present in the adenoids or tonsils of children from whom they had been removed surgically. Later other types were recovered from soldiers with febrile catarrh in the U.S.A. and also from children affected by an acute pharyngitis. An associated conjunctivitis in the children led to the term "pharyngo-conjunctival fever" for the children's disease but in recruits with febrile catarrh the eyes were frequently unaffected. An acute kerato-conjunctivitis in adults due to adenovirus infection has, however, been encountered both in the U.S.A. and in Britain particularly among shipyard workers. For the rest the British experience has confirmed the role of the adenoviruses in outbreaks in soldiers, the R.A.F. and in residential schools. Latent viruses have also been cultivated from the adenoids. It is fortunate that in spite of the multiplicity of the antigenic types of the adenoviruses, all of the strains develop in culture a soluble complement-fixing antigen. The latter can be used for examination of human sera to uncover infection by any of the fourteen or more serotypes of adenoviruses now known.

In the experience at Sheffield even after exclusion of the cases of influenza or of adenovirus infection, a substantial number of cases of acute respiratory disease remain of undetermined aetiology. Much the same can be said of endemic acute respiratory disease in the civilian population and it is now agreed by most workers that the adenoviruses do not appear to account for a large proportion of the burden of sickness due to respiratory tract infections.

The Common Cold

When we turn to the common cold, the aetiological situation has taken a new look since the description of the virus of Mogabgab. This was first recovered by a group of U.S. Naval Medical Officers who tested throat washings from patients with various acute febrile respiratory disorders in tissue culture. Another strain of this virus was recovered in 1956 by Price from nurses of the Johns Hopkins Hospital suffering from common colds. Price has recently claimed that this virus, which he calls J-H virus, was a cause of 30 per cent. of the colds at a home for babies and infants, and he has also prepared a vaccine from the virus which has some protective effect. The M.R.C. Common Cold Research Unit is testing the J-H virus in human volunteers at Salisbury. I cannot tell you more of this work except to say that the J-H virus will grow in tissue cultures in Britain but that it is a difficult agent to study. Even if it does account for one-third of all the colds from which we suffer, we are still without any clue to the cause of the remainder. Perhaps the common cold is a syndrome due to several distinct agents as is the case with the other forms of acute respiratory disease.

The Future

I will close this lecture by asking for patience to be exerted by those who seek to know more about the many acute diseases of the respiratory tract which are still in search of their causative viruses. Progress though slow is nevertheless steady and so long as laboratory workers are not hampered by insistent demands upon their time for diagnostic work, they will certainly succeed in a further clarification of the present obscure position. The almost bewildering complexity of the aetiological situation is at times discouraging particularly when virus species existing in many different antigenic varieties are uncovered. Respiratory viruses though less diverse than the Coxsackie agents are nevertheless fascinating agents to cultivate and the clinician can help by drawing attention to outbreaks with distinctive clinical characteristics and which appear to merit intensive laboratory study.

PAIN RELATED TO THE TEETH AND JAWS

BY

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Pain in and around the jaws is most commonly caused by pathological conditions related to the teeth and their supporting structures (*see* diagram) but it can also be caused by disease of other structures in these regions. It is not intended to discuss here such conditions as trigeminal neuralgia, which are well known to the medical practitioner, but rather to consider those local conditions which commonly cause confusion and difficulty in diagnosis.

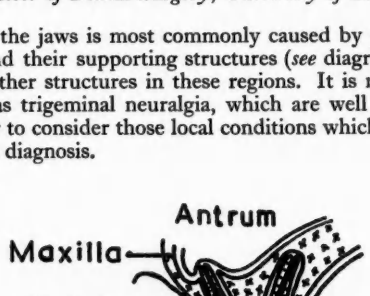

Diagram of a vertical section through the upper and lower jaw. Showing the structures mentioned in the text.

The precise diagnosis of "dental" pain is often a matter of considerable difficulty. Its localization by the patient is often very poor, making it difficult to demonstrate which tooth, if any, is responsible. It is quite common for the patient to point confidently to a particular tooth as the site of the pain when the teeth themselves are not at fault.

The causes of dental pain are most commonly dental caries and its sequelae, pulpitis, periodontitis and alveolar abscess. Next in frequency come the diseases of the soft tissues, notably gingivitis and trauma from ill-fitting artificial dentures. Another group arises from pathology within the jaws such as buried roots or cysts which have become infected. Finally, and much less frequently, there are the diseases of bone such as osteomyelitis, which affects the lower jaw almost exclusively in adults, and the diseases of the antrum which frequently cause pain related to the maxillary teeth. There are many others, but these are the common causes. Pain can also be referred

to the teeth from rather more remote areas of which the most common is the temperomandibular joint, while the reference of pain from one jaw to the opposing jaw is quite commonplace.

DENTAL CARIES AND ITS SEQUELAE

Dental caries, the commonest cause of pain is found in areas of stagnation, and the usual sites are the pits and fissures in the biting surfaces of the posterior teeth, the contact points between neighbouring teeth, and in later life, as the gums begin to recede, the necks of the teeth just above the gums. In these areas the stagnation of carbohydrates, particularly the refined forms such as sugar and sweets, results in their fermentation by bacteria with the production of acid. The acid attacks the enamel, causing decalcification, and burrows through the enamel from a comparatively small point of entry, undermining the enamel surface and often reaching the dentine before any cavity is formed. At this stage the damage is hardly visible by means of X-rays and is certainly not recognizable by clinical examination. Pain usually commences soon after the dentine is involved while the cavity is still very small, and the patient may notice slight pain on eating sweet or salt foods. The precise mechanism of this pain is not known, but it is unlikely that the pulp (i.e. "nerve") would be seriously involved at this stage. As the condition progresses, more dentine is involved and the caries approaches the pulp. The response to sweet foods becomes more severe until eventually the tooth becomes sensitive to thermal changes. This is an indication of early pulpitis, but even so this disease of the pulp may resolve with appropriate treatment. If the condition progresses further, the classical result will be the development of a severe pulpitis with lancinating pain of mounting severity, culminating in an excruciating pain lasting for half to one hour, after which there is a sudden relief. This relief is usually explained on the basis of strangulation of the pulp at the small foramen at the apex of the root where the venules become compressed by the engorged arterioles. At the same time, organisms invade the pulp, and the inflammatory process extends beyond the apical foramen into the periodontal membrane between the root and the bone. This is a periodontitis which in fact is a form of periostitis. The tooth is now tender to sudden pressure from biting or percussion, and as the inflammation progresses the pain becomes more continuous and more severe. It develops a throbbing character which is accentuated on lowering the head or lying down, and is most likely to become acute during sleep. At this stage, organisms have begun the formation of an alveolar abscess and soon the patient may have all the signs of pus under pressure. The tooth is raised in its socket and is knocked by every attempt at mastication with consequent pain. Eventually the pus will burrow through to the surface of the bone with relief of tension and of pain. Usually this pus presents as a "gumboil" within the mouth and over the root of the offending tooth; however, it may present at some distance from the tooth concerned and at times on the face.

This is the classic story as it occurs in the adult. Particularly in children and not uncommonoy in adults, the condition may subside into a chronic phase as a chronic pulpitis or periodontitis. In these circumstances the symptoms regress and the pain produced is often of a dull intermittent character which is difficult to diagnose. In such cases, acute exacerbation is not uncommon.

GINGIVITIS

Gingivitis, or inflammation of the gums, is fairly easy to recognize. Originally it is usually related to bad oral hygiene with excessive deposits of dental calculus (tartar) on teeth where they meet the gums. These cause a low grade chronic inflammation with swelling of the gum margins so that the gums project beyond the surface of the teeth and extend upwards on to the tooth surface. As they project beyond the tooth surface, they become subject to constant trauma from food in chewing and as they now overlap the tooth surface they create a fine space or pocket between themselves and the

teeth in which food and calculus can stagnate, causing further irritation and inflammation. This may remain chronic for many years, but the irritation within the pocket causes ulceration at its base, deepening the pocket and producing an inflammation in the periodontal membrane which leads to its gradual destruction. This is *periodontitis simplex*, or the common type of what is known as pyorrhoea. The pain from this condition is rarely severe and therefore the patient may be unaware of it for quite a long time; but at any stage there may be an acute exacerbation with acute gingivitis, visible ulceration, bleeding from the gums, marked foetor oris, and intense pain; this is known as ulcero-membranous gingivitis, Vincent's stomatitis or Trench mouth. In severe cases the disease may spread to the other muccous surfaces of the mouth, producing ulcers, and the patient may be quite ill with a high temperature, rapid pulse and severe malaise. Perhaps it should be stressed that this rarely arises except as a complication of existing gingivitis, and therefore treatment must include the treatment of the underlying bad oral hygiene. The patients often have some form of chronic ill-health which should also be treated appropriately.

The lesions of gingivitis and pyorrhoea are usually generalized throughout the mouth, but natural pockets around erupting teeth may give rise to a local gingivitis with infection of the pocket. This is common with eruption of the third molar (wisdom tooth). It is known as *pericoronitis* and occurs most frequently around the crown of an impacted tooth which has partially erupted but can erupt no further. Classically it causes very severe pain of the throbbing type with considerable swelling, especially of the gum over the tooth, so that mastication is very painful. The pain and swelling commonly cause a reflex trismus or limitation of opening of the mouth, which may be partial or complete. As with the other types of gingivitis it often becomes chronic and subject to acute exacerbations.

Absence of teeth is no guarantee that pain is not dental, for roots are still unfortunately left behind, teeth may remain unerupted for many years, or cysts may become infected from local or haematogenous sources, when they produce symptoms similar to those of acute or chronic dento-alveolar abscess.

OSTEOMYELITIS

Pain caused by osteomyelitis must be mentioned to distinguish it from that caused by an alveolar abscess. Almost invariably in osteomyelitis the pain is more diffuse and usually more severe. The teeth in the region are often tender to percussion, but usually several teeth are involved, whereas with an alveolar abscess, although neighbouring teeth may seem tender, the tenderness is usually much more acute in the tooth causing the abscess. Swelling is usually much greater and more diffuse in osteomyelitis, and the systemic reaction as shown by the pulse, temperature and general condition is usually much more severe. The radiographic appearances are usually easily distinguished. The abscess shows a localized area as distinct from the more diffuse involvement of bone in osteomyelitis, but it must not be forgotten that the appearance of radiographic evidence is a comparatively late finding in both of these conditions, taking approximately 10 days to develop. Except in very young children osteomyelitis is found almost exclusively in the mandible.

Disease of the antrum

In the maxilla the commonest confusion of diagnosis is caused by diseases of the antrum, which may give rise to pain related to the teeth. Because the roots of the molar teeth are close to the antrum, any inflammation in this region may involve the periodontal membrane of the teeth, resulting in tenderness on biting and percussion. Here again, usually a group of teeth is affected as distinct from the more localized pain of periodontitis or alveolar abscess caused by disease of one tooth. Each year a few cases of antral carcinoma find their way to the dental hospital for the diagnosis of "dental" pain, often only after several teeth have been removed without relief. The carcinoma has, of course, advanced during this time.

Other local causes of pain

Of the other diseases affecting the soft tissues of the mouth and causing pain, three deserve mention. Trauma from ill-fitting or even from comparatively well-fitting dentures is very common, and the ulcers and painful areas produced may be small but are often very painful. As would be expected, they usually heal rapidly when the dentures are left out of the mouth for a few days. The second condition is aphthous stomatitis in which very painful, recurrent, small round ulcers are found in the mouth. These persist for one or two weeks, sometimes longer, and then heal spontaneously, to be followed by other batches at fairly regular intervals. Little is known of the cause though it seems probable that some are due to a virus like that of herpes simplex. It is probably a heterogenous group, and is difficult to treat. The best results are usually obtained by attention to oral hygiene and general health.

The third condition is lichen planus; it has received considerable attention recently because it is much more common than was previously supposed. It may cause a severe burning sensation in the mouth with very little to be seen. The oral manifestations may vary considerably over a period and it is therefore often necessary to examine the patient two or three times at intervals before the lesions can be found. Though it is usually a generalized disease of skin and mucous surfaces it can occur in the mouth without any lesions being found on the body. The lesions take two main forms. Commonly they appear as white dots or streaks which are often arranged in a lace-work pattern but may simulate an early leukoplakia. Less commonly there may be superficial erosions of the mucosa which are very painful and are usually associated with some of the white patches.

Temporo-mandibular joint

One of the conditions associated with the teeth and causing dental pain, though comparatively remote from them, is arthrosis of the temporo-mandibular joint. The precise nature of the lesion within the joint is not clearly understood. The condition usually commences with clicking in the joint, which is at first noticed only by the patient though later it may become audible to others. This may be accompanied by some pain and limitation of movement of the mandible from the beginning, but at times it continues for some years before the symptoms are severe enough to cause the patient to seek treatment. Sooner or later either this clicking becomes annoying or there is an acute exacerbation with severe pain often associated with temporary but complete limitation of movement so that the patient seeks advice. In the acute case the pain is usually fairly localized over the temporo-mandibular joint, but in the more long standing chronic cases the pain is intermittent, of varying severity, and may be referred to the temporal and parietal regions, the jaws, or to the tongue. There may be some tinitus. When all of these signs are present, it is known as Costen's syndrome, but this is rare. Much more commonly, the pain is referred to one region only, often one of the jaws. Fortunately, the diagnosis of these cases is assisted by the clicking and the abnormal movements of the mandible which are usually present. The condition is frequently related to abnormalities of the dental occlusion which can be treated, but it can arise indirectly as a result of true dental pain causing abnormal excursions of the mandible to protect the offending teeth. Diagnosis in such cases may be difficult.

It is common knowledge that pain arising from the teeth is frequently referred. This reference is usually from one molar to another in the same or opposing jaw, but it may spread over wider areas throughout the distribution of the second and third divisions of the trigeminal nerve. In acute periodontal disease, pain is fairly readily localized by the patient, but in more chronic lesions, particularly of the pulp, pain is poorly localized, and it is often referred widely.

DIAGNOSIS

It must be obvious from this brief account of some of the possible causes of "dental" pain and from the frequency with which true dental pain occurs that diagnosis is often difficult.

There is no rule of thumb which can be applied. Only a good history and a thorough examination can guard against the many pitfalls.

The most important point in the diagnosis is to build up from the history and the present symptoms, the natural history of the condition, which should indicate the type of pathology to be considered even if it does not immediately give a conclusive answer. After this there are the special methods of examination of the teeth used by the dental surgeon to disclose caries, pulpal, periodontal and gingival disease, and the more usual examinations for antral or bony disease and for examination of the soft tissues. An elementary point which is worth mentioning is that many small lesions of the teeth and soft tissues are missed by failing to dry the tissues before examination, so that they remain obscured by saliva with its bubbles and reflections of light.

In the more obscure cases, the diagnostic injection is often of the greatest value. By means of regional block and infiltration anaesthesia which is easily produced by any dental surgeon, the source of the pain can gradually be localized to or excluded from the jaws. This is particularly of value in dealing with pain which is thought to be of psychogenic origin. The patient is asked to note the time at which relief of pain occurs and its precise duration. Saline injections can also be used to differentiate between functional and organic pains. The results are sometimes surprising.

Nothing has been said of the pain which arises after injection or extraction in the course of dental treatment. Here the cause is usually quite obvious though one must be careful, for with the prevalence of dental disease it is not uncommon for so-called post-operative pain to be caused by a cavity in a neighbouring tooth.

Any patient with pain arising after dental treatment should always be referred to the dentist as soon as possible. He knows only too well that such things happen and should always be willing to treat these patients. He is also in the very best position to know the probable causes of the pain.

TREATMENT

The diagnosis of "dental" pain is often very simple but it is rarely wise to undertake treatment without a thorough examination of the teeth and mouth. It is not sufficient to look in the mouth and advise total extractions because the teeth are obviously stained and dirty, for in such cases attention to oral hygiene can often produce surprisingly good results, and it is often quite impossible to discover what disease is present until the teeth have been cleaned. Usually the best course is to tell the dental surgeon of the problem and ask his advice.

The treatment of the many conditions which have been mentioned is much too big a subject to be discussed here, except to say that so few of the conditions causing dental pain need treatment with systemic antibiotics that their use is rarely justified before a diagnosis can be made. In fact, their use often makes diagnosis more difficult. Local use of antibiotics carries risks and is so rarely of value that this is best avoided altogether. When a cavity can be found which is related to the pain, oil of cloves applied on a pledget of cotton wool in this cavity will often bring considerable relief, and should this fail, the common anodynes will usually succeed temporarily until dental assistance can be obtained.

SUPPORTIVE TREATMENT OF ACUTE COR PULMONALE DUE TO MASSIVE PULMONARY EMBOLISM

E. A. W. HOUGHTON, M.B., CH.B.

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Pulmonary thrombo-embolism may cause a variety of clinical features. Generally, however, cases fall into three main groups; (1) those in which no immediate symptoms occur, but who may develop subacute cor pulmonale if embolism is recurrent; (2) those in which demonstrable pulmonary infarction occurs with absent or minimal circulatory signs, and (3) those cases in which there is an acute and profound circulatory disturbance, right ventricular failure predominating. The latter constitutes the syndrome of acute cor pulmonale.

The usual clinical features of acute cor pulmonale are pain or a sense of oppression in the centre of the chest, peripheral cyanosis or pallor, hypotension, raised jugular venous pressure and signs related to right ventricular and pulmonary artery dilatation. Typical electrocardiographic changes occur.

While pulmonary embolism is a common condition, the proportion of cases in which cor pulmonale occurs is small. Short (1952) in his survey of 113 cases, classified 16 as "massive", and among 34 cases seen by the present author in a period of a year 9 were in this category. In an acute hospital of 500 beds, 10 fatal cases are to be expected each year (Marks *et al.*, 1954).

Attention in recent years has been focused upon the problem of the prevention of peripheral venous thrombosis, particularly in the post-operative period. There has been a relative neglect of the management of the emergency of massive embolism. This may be partly due to an attitude of pessimism as to the outcome and the fact that in most hospitals the initial management is often in the hands of junior medical staff inexperienced in the treatment of this condition.

Treatment is primarily supportive. Measures advocated include analgesics, vagolytic agents, antispasmodics, myocardial stimulants and more recently pressor agents particularly l.nor-adrenaline. Anticoagulant therapy and possibly venous ligation may be considered as secondary measures to prevent further embolism.

The following case is reported as it illustrates many of the practical problems of management, and the success of vigorous action towards maintaining a normal blood pressure.

CASE REPORT

A woman aged 68 years was admitted to Southmead Hospital, Bristol, on 24th November, 1953, following a haematemesis. She was known to have a chronic duodenal ulcer and had had several haematemeses before. On examination on this occasion a mass was palpable in the left iliac fossa. After cessation of the alimentary haemorrhage, sigmoidoscopy was performed, but only the lower 10 cm. of bowel was visible owing to spasm. A "blind" biopsy was taken which was reported as showing "columnar cell adenocarcinoma". Operation was advised but refused by the patient. A barium enema examination was unhelpful as the enema was not retained.

The patient was readmitted six months later on account of left-sided abdominal pain and vomiting. On 5th May, 1954, a laparotomy was performed by Mr. J. A. Pocock and a mass was found to be present in the sigmoid colon. A transverse colostomy was fashioned and the wound closed. On the eight post-operative day the patient was being wheeled along the ward when she suddenly experienced severe upper abdominal pain, tightness in the chest, and breathlessness. Examination revealed that she was cyanosed and shocked. The pulse was 130 per min., and systolic blood pressure 70 mm.Hg. The neck veins were engorged and pulsating. There was increased pulsation over the precordium to the left of the sternum at the level of the second and third interspaces. Breath sounds were reduced at the lung bases. There were no clinical signs of venous thrombosis in the legs. A clinical diagnosis of massive pulmonary embolism was made which was supported by an electrocardiogram. This showed high 'P' waves, a 'Q' wave in lead III, partial right bundle branch block, flattened 'T' waves and depression of the S-T segment.

Pethidine 100 mg. and methylamphetamine ("methedrine") 30 mg. were given intramuscularly, heparin 10,000 international units (77 mg.) intravenously and ethyl biscoumacetate ("tromexan") 900 mg. orally. Although there was slight relief of pain, the hypotension persisted and so, an hour after the onset, an intravenous infusion of 5 per cent dextrose with 4 ml. of 1:1000 l.nor-adrenaline per 500 ml. was commenced. This gave a concentration of 8 μg. per ml. There was an immediate response, the blood pressure rising to 130/100 mm.Hg. By regulating the speed of the infusion to 15–20 drops per minute the blood pressure was maintained at 110/90 mm.Hg. Papaverine ½ gr. (30 mg.) was also given intramuscularly. The serum prothrombin level was kept between 30 per cent and 60 per cent of normal by varying the dose of the anticoagulant.

Recurrent chest pain was a distressing feature during the following three days. This did not respond to conventional doses of pethidine or amidone, but rapid temporary relief followed introduction of 2–5 ml. of 2 per cent procaine hydrochloride into the infusion. Considerable difficulty was experienced in maintaining the l.nor-adrenaline infusion, for whenever it was slowed down appreciably the blood pressure fell and the patient lapsed into coma. Following leakage into the tissues at the original infusion sites in the anticubital fossae there was considerable local oedema, pain and tenderness. This was followed by discolouration of the skin which eventually sloughed. Skin loss was made good by skin grafting at a later date. Ouabain was given in doses of 1 mg. intravenously at six-hourly intervals during the first 24 hours but produced no noticeable improvement in the pulse or the patient's general condition.

During the fifth day of treatment it was found possible gradually to reduce the rate of the l.nor-adrenaline infusion without the blood pressure falling, and it was eventually discontinued on the sixth day.

Three weeks after the embolic incident the patient was ambulant and symptom-free apart from some breathlessness on exertion. The electrocardiogram gradually returned to normal, and the venous pressure, as judged by the neck veins, gradually fell. The heart remained clinically enlarged for several months but its size eventually returned to within normal limits. No definite signs of pulmonary infarction appeared in the chest clinically or radiologically. On the 28th July, 1954, the second stage of the sigmoid colon resection was carried out and was uneventful. Microscopical examination of the operation specimen revealed no sign of neoplasia, the appearances being consistent with diverticulitis.

The patient has continued in reasonably good health, apart from symptoms attributable to her peptic ulcer, and has not experienced any further symptoms referable to the cardiovascular system.

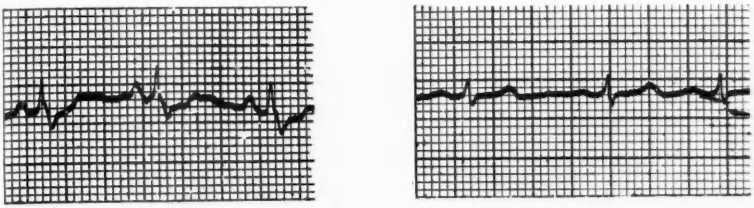
DISCUSSION

Diagnosis in this case was not difficult as the symptoms and signs were typical. However, similar peripheral circulatory failure may be produced by other conditions, including myocardial infarction, concealed haemorrhage, supra-renal haemorrhage and severe septicaemia. Attention to the cardiac signs and the electrocardiogram will usually produce sufficient evidence of right ventricular failure or 'strain' for a diagnosis of acute cor pulmonale to be made.

The exact mechanism of the circulatory changes commonly seen is not perfectly understood. Experiments in animals in which the pulmonary arteries have been occluded in varying degree by ligature or by artificial emboli, have shown that it is necessary to obstruct 60–85 per cent of the total cross-section before the systolic blood pressure falls or before signs of right ventricular failure can be detected (Gibbon *et al.*, 1932). The term "right ventricular failure" is a misnomer, as the ventricle shows forceful action in its attempt to maintain a head of pressure so as to overcome the obstruction. At autopsy the chamber is usually engorged and the pulmonary artery dilated; when these features are not present vaso-motor shock, by reducing the return of blood to the right heart is probably responsible.

Fatal cases have been reported in which a relatively small embolism was present at autopsy, occupying only a small proportion of the pulmonary artery (Fowler and Bollinger, 1954). Reflex coronary artery spasm may play an important part in such cases. Attempts to prove this by animal experiments have been inconclusive, however. De Takats *et al.* (1939) found that atropine and papaverine apparently had a protective effect in dogs, but Malinow *et al.* (1946) state that bilateral vagotomy fails to influence the electrocardiographic changes. However, atropine and/or papaverine are still recommended in the standard textbooks (Brooks, 1952; Wood, 1956). In the case described papaverine did appear to relieve pain, but was accompanied by a fall of

PLATE I



Lead II of Electrocardiogram: (*a*) Three hours after massive pulmonary embolism.
(*b*) Three months later.

Skin necrosis following l-nor-adrenaline intravenous infusions.

blood pressure on one occasion when ½ gr. (30 mg.) was given intravenously. The relief of pain by procaine hydrochloride was first noticed when 2 ml. of 2 per cent solution was given intravenously to relieve venospasm when the intravenous infusion was behaving erratically. Its use has not been previously recorded in the literature for this specific purpose.

Churchill (1934) in his classic description of massive pulmonary embolism emphasized the potential harm of venesection which has been advocated in order to "take the load off the right ventricle". Wood (1947) has pointed out that the raised venous pressure is beneficial. For this reason digitalis is contra-indicated, while a strophanthin preparation, such as ouabain, has theoretical advantages as it is said to stimulate the myocardium without lowering the venous pressure. Rapidity of action is also in its favour, and ouabain in particular appears to exert a pressor effect in full therapeutic dosage (McMichael, 1950).

There is evidence that anticoagulant drugs will reduce the likelihood of further embolism (Barker *et al.*, 1945, Cosgriff, 1950), although fatal embolism may occur during anticoagulant treatment (Farris, 1954). A further reason for their use is that they prevent the formation of propagation clot beyond the impacted embolus. In this connection attention should be drawn to the work of Cummine and Lyons (1948) and Dew (1953) who suggest that primary thrombosis of the pulmonary artery is more common than is usually recognized. Burt (1954) reports that propagation clot is infrequently found in autopsy cases when anticoagulants have been used but she records having seen it in fatal cases when anticoagulants have not been employed.

Venous ligation as a prophylactic measure against further embolism is losing popularity (Farris, 1954); it is a gamble and late sequelae may be disabling if the inferior vena cava is tied (Shea *et al.*, 1951). This operation also has a significant mortality (Riddell and Kirtley, 1952), also it has been shown that the incidence of fatal embolism is not reduced by either prophylactic or therapeutic vein ligation (Lillie *et al.*, 1949; Kirby and Fitts, 1950).

The most important aspect of treatment in this case was undoubtedly the action of l.nor-adrenaline in raising and maintaining the blood pressure. This substance, which is normally present in the adrenal medulla and at the synapses of postganglionic sympathetic nerves has been widely used in a variety of hypotensive states since its introduction for this purpose by Goldenberg *et al.* (1949). Its use in acute cor pulmonale has been reported by Wolff (1954), de Swiet (1955) and Sibthorpe (1955). The mechanism of the beneficial action in such cases probably lies in the improved coronary circulation caused by active vasodilatation of the coronary arteries and by raised aortic pressure (von Euler, 1955). The concentration of the infusion used depends upon the individual response. de Swiet found that a concentration of 64 ml. of 1:1,000 solution per litre was necessary in his case so as to avoid risk of overloading the circulation with too large a volume of dextrose solution. Therapy must be continued until the balance of ventricular input and output is restored. Presumably this becomes possible through packing of the thrombus against the vessel wall and the gradual relaxation of any arterial spasm which may be present, together with improved function of the myocardium. The ganglion-blocking effect of l.nor-adrenaline which has been described by Burn (1956) and others, and recently emphasised by Mushin (1957), was not evident in this case when the drug was discontinued. During the long period of l.nor-adrenaline "dependence" there was ample evidence of a central cause for hypotension without incriminating the drug. However, the precaution was taken of gradually weaning the patient from the nor-adrenaline when her general condition had improved.

Skin necrosis following intravenous administration of l.nor-adrenaline has been reported by Greenwald *et al.* (1952), Bergmann (1953) and Humphreys *et al.* (1955). The latter authors discuss the possible causes in detail, and conclude that impaired peripheral circulation and a high local concentration of the drug is responsible. They advocate percutaneous administration into a large vein together with frequent

introduction of papaverine and procaine into the vein to relieve local spasm. All these details were employed in this case but skin necrosis occurred. Constant vigilance and an awareness of the possibility of the complication are probably the most important factors in prevention.

SUMMARY

The treatment is reviewed of acute cor pulmonale due to massive pulmonary thrombo-embolism.

A case is described in which the use of a pressor agent, l.nor-adrenaline, appeared to play a prominent part in the successful outcome.

Early recognition of the circulatory features of this condition and its differentiation from other causes of shock is essential. The meticulous maintenance of normotension is the basis of treatment at the present time.

Further experimental and clinical research is needed in this subject.

ACKNOWLEDGMENTS

I am indebted to Mr. J. A. Pocock and Dr. H. J. Orr-Ewing for their permission to publish details of this case.

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ACCIDENTAL POISONING WITH THE ANTIHISTAMINE DRUG "HISTANTIN"

A Clinical Pathological Conference of the University of Bristol Medical School.

CHAIRMAN: PROFESSOR T. F. HEWER

Professor Hewer. I will ask Dr. Apley, who looked after this child, to give us the clinical history.

Dr. John Apley. Let me first tell you about the family of this little girl, an only child, who died in hospital three days before her first birthday. The father is a man in his early thirties, who owns a shop. The mother is a kind and pleasant woman of some twenty years of age. They live in a small house over the shop. Mother has a mild skin disorder for which, unfortunately, as events will show, she was taking antihistamine tablets ("Histantin").

She came into the room where Jane had been left playing one day and found her eating some tablets. Mother thinks that nine were swallowed in all. The child was seen by a doctor about one hour later. There had been no vomiting and Jane seemed well, so the doctor advised that she be taken home to rest. Fifteen minutes later she started to vomit and had generalised convulsions.

She was immediately taken to the local hospital where her stomach was washed out with bicarbonate of soda solution, approximately one-and-three-quarters hour after ingestion of the tablets. While this was proceeding the doctor telephoned me. With a recent previous experience of such a case (a child who also died despite treatment) I advised that Jane should be brought into hospital immediately. The journey was a long one and she arrived in hospital some four hours after swallowing the tablets.

On admission she was slightly cyanosed and generalised muscular twitching was seen. Her temperature was 100·8°. The heart rate varied between 80 and 170 and was irregular (presumably owing to the so-called quinidine effect of the drug). Moist sounds were heard all over the lungs, an ominous sign which carries a very grave prognosis in this condition.

TREATMENT AND PROGRESS

The stomach was sucked out, and some paraldehyde was injected intramuscularly. She was put in an oxygen tent. We were faced here with the problem of dealing with a condition in which central nervous depression may prove lethal, yet nervous stimulation may produce fits which are themselves highly dangerous. The problem of stimulants versus anticonvulsants is an insoluble one, but in this case, as in other cases of poisoning, the usual rule is to treat the immediate disturbance rather than the underlying condition. Some forty-five minutes later, when the generalised twitching was still marked, she was given rectal thiopentone.

Three hours after admission the heart rate was rapid and irregular, she was vomiting thick brown material, and the twitching persisted. After a further small rectal injection of thiopentone the twitching ceased, her colour became better and the respiratory rate was lower.

At this stage, the case was discussed with Professor Heller, who kindly came to the hospital to see the child. Seven hours after admission convulsions recurred and further mild sedation was attempted. In spite of treatment the twitching persisted, her temperature rose to 105°, her general condition deteriorated and she developed peripheral circulatory failure and died some thirteen hours after admission to hospital.

Professor Hewer, shall I say a few words now or later about the natural history of poisoning in children?

Professor Hewer. I think we should like to hear it now.

Dr. Apley. In paediatrics, as in general medicine, we tend to congratulate ourselves on the fact that the incidence and dangers of many disorders, especially infections, are being rapidly controlled. Poisoning and accidents, in the home or on the road, are unfortunately not decreasing. I may add that dangerous iatrogenic disorders also seem to be increasing.

Medicines or pills are the cause of about half the deaths in children due to drugs. Only very rarely is this due to an error or accident by the doctor or chemist. The others are due to the child swallowing liniments, cleaners, polishes, pesticides, etc.

The most dangerous room in the house is the kitchen, followed in order by the bedroom, bathroom, and living room. The type of children affected can be divided into two groups. The first, and perhaps the most tragic, is the group of normal toddlers with initiative and an urge to explore. In children, of course, the tongue is an organ of sense. Any moveable object may be put into the mouth, but is often spat out again unless it is tasty. The difficulty is that more and more drugs are being made attractive to look at and palatable to swallow. Some of the NHS prescriptions are flavoured with extract of cherries, and so on, and some tablets are so like "Smarties" and "Hundreds and Thousands", used to decorate cakes, that any child might be expected to gobble them up (here a coloured slide, lent by Dr. Oppé, was shown to illustrate the similarity between tablets and sweets, (Plate II)). The second group, possibly larger than the first, is made up of infants and toddlers who eat anything. They are fierce feeders, both off the bottle or the breast, and will chew thumbs, fingers or anything they can get hold of. This is said to be a form of self-gratification and has been claimed to be part of a widespread psychological disturbance.

Professor Hewer. Before we have any discussion of this case I shall ask Dr. Halford to tell us his autopsy findings.

Dr. M. E. H. Halford. The autopsy does not give us very much additional information. There was some dehydration, with inelasticity of the skin. The liver, although normal in size, was flabby and pale. Histological examination confirmed that there was diffuse fatty change and also some early centrilobular necrosis. The kidneys showed advanced cloudy swelling, but this may have been a post-mortem change since the autopsy was performed twenty-three hours after death. The brain was moderately oedematous, but there were no petechial haemorrhages.

There was no evidence of pre-existing disease or congenital deformity.

The Registrar-General's returns for England and Wales show the changing incidence of fatal poisoning in children under ten years of age, emphasising Dr. Apley's comments. During the period 1931–1935 the commonest causes were:

Belladonna	8 cases	Disinfectants	5 cases
Caustic soda	7 „	Camphor	5 „
Strychnine	6 „	Aspirin	3 „

From 1950–1952 the list is very different:

Ferrous sulphate	24 cases	Strychnine	12 cases
Antihistamines	19 „	Lead	7 „
Aspirin	15 „	Oil of Wintergreen	6 „

When allowance is made for the shorter second period, the increase is considerable, and antihistamine drugs are second on the list.

There are two points of interest in the course of the illness of this child. One which emerged during the inquest was that the first abnormality noticed was a vacant expression. This has been observed in other reported cases of antihistamine poisoning. The second point is the occurrence of vomiting; this is unusual. In the one reported case of Histantin poisoning[3] vomiting also occurred. Perhaps Professor Heller will be able to explain these points. The reported case was successfully treated by light sedation atropine and amphetamine, although a large amount of the drug (900 mgm.) had been ingested.

Dr. Apley. I don't believe Dr. Halford told us anything about the lungs.

PLATE II

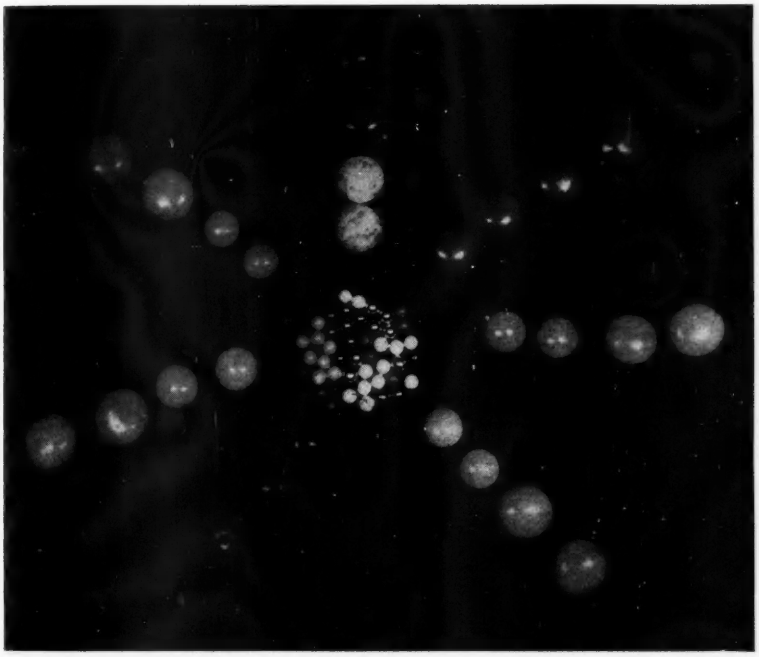

Plate II. *A collection of drugs and sweets arranged by Dr. Oppé to show the close similarity between them.*

Dr. Halford. The trachea and bronchi contained a small quantity of slightly bloodstained watery fluid. There was no pulmonary oedema. The histology of the lung showed the bronchiolar epithelial cells to be distended with mucin. This increased secretion, in the absence of pulmonary oedema could account for the accumulation of fluid in the upper respiratory tract. This excess of fluid has been reported in other cases of antihistamine poisoning.

Professor Hewer. If the baby's mother had not found the bottle of Histantin, and realised that the baby had swallowed some, the clinicians and the pathologist would have had great difficulty in determining the cause of the illness. I should like to put it to Dr. Halford that he would have had no clue.

Dr. Halford. It would be very difficult indeed to diagnose. The vacant stare, lack of vomiting, muscle twitching with some convulsions and increased upper respiratory tract secretions might suggest antihistamine poisoning if one happened to think of it. I could not have proved it at autopsy without chemical analysis.

Dr. Apley. Professor Hewer's remark raises a very important issue. In this case it was obvious that the child had swallowed something poisonous, but if the evidence has been destroyed the diagnosis must often be completely unsuspected. I saw a most tragic example two or three years ago, when I was visiting a large hospital, a long way from here, to see some cases. While I was discussing them with the local paediatrician an infant was brought in, vomiting blood and moribund. He died shortly afterwards. I was told that only one month previously his elder brother had died, also after vomiting blood. The possibility of poisoning had not been confirmed; on post-mortem examination acute haemorrhagic gastritis was found, and it was suggested that this had been due to a streptococcal infection.

We took the father into a quiet room and cross-examined him. Eventually it came out that the mother was pregnant again and was taking ferrous sulphate tablets. The local doctor was telephoned, hurried round to the house, and found that a large number of ferrous sulphate tablets were missing. Ferrous sulphate poisoning, previously unsuspected, had killed both the children.

Professor H. Heller: Did you find any reference in the literature, Dr. Halford, to lesions in the liver?

Dr. Halford. In the reported cases, post-mortem findings are indifferently recorded, and sometimes not mentioned. In others gross changes are described and very few give a full histological description. The liver is mentioned as being congested in one case but this was part of a generalised venous congestion. Findings in other cases include cerebral oedema with petechial haemorrhages, petechiae in the thymus and pericardium, and, as I have already mentioned, severe upper respiratory tract catarrh.

Dr. A. C. Hunt: I would like to make a comment on why the Coroner did not have an analysis made after this post mortem. In this case he is quite justified from his point of view in not needing a chemical analysis, as the facts are quite clear. In some cases, for example when the amount of a drug taken is not definitely known, and if there is any natural disease that might have influenced death, it is most important that the pathologist should insist on an analysis, made either by himself or by the Forensic Science Laboratory.

Professor Hewer. Will Professor Heller tell us about the toxic effects of the antihistamines?

Professor Heller: I am afraid there is comparatively little I can contribute to this interesting discussion. However, two remarks may be worth making: First, the absence of vomiting in most patients suffering from poisoning with antihistamines is very likely due to a depressant effect of the drug on the so-called chemoreceptor trigger zone in the floor of the fourth ventricle. You will remember that some of the antihistamine compounds as well as chlorpromazine (to which they are chemically closely related) are actually used for their anti-emetic properties. There is, on the other hand, some indication that antihistamine may have a direct irritant effect on the gastric mucosa. For instance, Drs. Ashford, Smart and I[1], in an investigation concerned

with the effect of antihistamines on gastric secretion, found that ulcer patients did tolerate these drugs rather badly and responded occasionally with an increase in gastric secretion. One may therefore conjecture that vomiting in a poisoned patient depends on the "competition" between central and peripheral action of the antihistamine drug. Secondly, the action of the antihistamine on the eyes has been mentioned. One would expect such effects since the antihistamines have quite pronounced atropine-(or perhaps more correctly hyoscine) like properties.

This brings me to central effects of the antihistamines. They, as Dr. Apley has already stressed, seem to consist in a curious mixture of depression and stimulation. It has been suggested that the stimulant action is related to the atropine-like side effect and it is of course true that belladonna poisoning may lead to central excitation and pyrexia. But it should not be forgotten that antihistamines are also quite strong local anaesthetics and that local anaesthetics like cocaine and procaine have also a pronounced stimulant effect on the central nervous system. However, remembering the patient under discussion whom—thanks to the kindness of Dr. Apley—I was able to see in the Children's Hospital, and the descriptions of some published cases of poisoning with antihistamines, I have the impression that the central effects of these toxic doses consist in a curious mixture of depression and stimulation of different parts of the brain. One is reminded of morphine although the cerebral localisation of these effects is obviously different. The therapeutic problem is therefore—as already mentioned—very difficult. One really does not know which drugs to use to combat the toxic effects on the central nervous system. The history of this patient which, alas, resembles only too closely that of many other cases of antihistamine poisoning in children, has led me to the conclusion that more experimental work is needed to investigate the effects of toxic doses of antihistamines. I have, in fact, last week proposed this subject to a Ph.D. candidate. I think that we shall only arrive at a rational therapy if we know which parts of the central nervous system are differentially affected by toxic doses of antihistamines. Judging again from the comparison with morphine, we need something like nalorphine that is to say a competitive inhibitor.

Lastly, a word about a further feature which was rather prominent in this patient, namely the effects on the heart. The quinidine-like action of antihistamines was first discovered in experiments on the isolated rabbit auricle. The present case suggests that it may not only be a pharmacological curiosity but a serious toxicological feature which requires therapeutical efforts.

Question. Is it logical to use histamine as a neurotransmitter for treatment of the cerebral depression?

Professor Heller. There is good evidence that histamine is present in certain nerves but little evidence that it occurs in the central nervous system. Thus, it is unlikely to have a function as a central humoral transmitter. It is therefore difficult to see any beneficial effects which injections of histamine could have in antihistamine poisoning so far as the central nervous system is concerned. It may be useful, however, to find out whether any of the peripheral effects of the antihistamines could be antagonized by histamine injections.

Dr. Apley. Some say that histamine is useless and others that it should on no account be given.

Dr. W. O. Spence. What would be the dosage of antihistamine which should alert the general practitioner to take immediate action? I had a case two weeks ago of a toddler who swallowed about one ounce of Elixir Benadryl (about four times the correct dose); I reassured the mother and left her to report again if any signs appeared, but it would appear as though it would have been safer to have made the child vomit.

Professor Heller. It is difficult to lay down maximum doses for the various compounds with antihistaminic effects, not only because these substances have a different potency[2] but also because the sensitivity of different patients to the same antihistamine drug varies widely. It may even vary considerably in the same patient according to his state of health. May I refer you to the work of Warin[4] who has shown by applying intra-

dermal wheal tests that a patient may not be affected by the "ordinary" dose of an antihistaminic, but may need a very much larger dose to affect his allergic condition. However, I should like to stress that the wheal test in such a case is essential.

Dr. B. E. McConnell. It is recorded that this child swallowed the drug at about 2 p.m. This was presumably after a meal. Would not an injection of apomorphine have produced satisfactory emesis?

Professor Heller. I would assume that apomorphine would be of value at an early stage, e.g., before central depression has occurred. But I think that apomorphine would be dangerous at a later stage since it has a medullary depressant action itself.

Dr. T. E. Oppé. Gastric lavage is much more sure and also safer because with the use of an emetic there is a danger of aspiration pneumonia.

Professor Heller. I quite agree that an emetic may be dangerous. In that connection I think the simplest way of producing vomiting in a child, namely by insertion of a finger down its throat, should not be forgotten.

Dr. A. J. Webb. Emetics are very unpopular in the Casualty Department and gastric lavage is always performed.

Dr. Halford. Mention has been made of the minimum lethal dose of antihistamines. In an account of a published series of fatal cases I found the smallest fatal dose was 100 mgm. of methapyrilene hydrochloride ("Thenylene") for a child of sixteen months: this is just twelve times the normal dose for such a child and only twice the adult dose.

REFERENCES

[1] Ashford, C. A., Smart, G. A., and Heller, H., 1949, *Brit. J. Pharmacol.* **4**: 157.
[2] Bain, W. A., 1949, *Proc. Roy. Soc. Med.* **42**: 615.
[3] Gill-Carey, M. C., 1954, *B.J.M.*, **i**: 688.
[4] Warin, R. P., 1950, *Brit. J. Derm.*, **62**: 159.

An Apology to Dr. G. E. F. Sutton

Dr. Sutton points out that at the Clinico-Pathological Conference published in the January number of this *Journal* he is quoted as saying "These so-called postural deformities occur in children with malnutrition. They are sub-rachitic". Yet what he actually said was that in former days the mild cases of postural deformity were often sub-rachitic.

We apologise to Dr. Sutton for reporting him incorrectly, and for omitting to send the text to him for correction before it was published.

Editor.

Correspondence

DEAR SIR,

Medical Education

It has been said that our greatest responsibilities lie with the next and subsequent generations: there is no exception in the case of the medical profession. It is inherent in our tradition that, even though we may not transmute, we shall transmit our knowledge and experience in a Hippocratic reverence: "Pure and holy will I keep my Life and my art".

Medical Education has never been static. To thoughtful people there is nearly always some focus in need of "fundamental reconsideration" in relation to the "aim and purpose" of the medical curriculum. It is implied in Hippocrates Aphorism 1. "The art is long; the occasions sudden; the judgements difficult: neither is it sufficient (only) that the physician do his office—the patient and his attendants must do their duty and the externals must likewise be well ordered."

Studentship and practice shall, therefore, have a wholeness and a comprehension much of which is, perhaps, more nearly related to a liberal understanding and application of the humanities than to a varying (and expansive) pharmacopoeia (official and unofficial). There is nothing new in this: the only difficulty is to achieve this in the face of conflicting demands. From the earliest days we should do all we can to encourage ourselves as teachers to the discovery of an increasing unity in the apparent diversity of Nature. Medical education could more wisely be centred on a concept of human biology, and man's place in nature, and his mental health. But these general principles must be made throughly apparent to the student in his earliest acquaintance with his teachers. He can, by an infectious enthusiasm, soon come to understand that the most searching clinical problems require the greatest reference to basic science. The dichotomy—pre-clinical and clinical—is obsolete: there must be a two-way system in thought and practice. Our awareness of the dividing lines between the normal, the near-normal and the abnormal is tuned up by the marginal facts of physiology and pathology.

In my experience, the student is more attracted in clinical discussion by rather frequent and relevant reference to the normal. I sense a growing concern of the students for a much wider perspective in the patient's problems and a willingness for more searching enquiry into the basic causes of disorder. There is even an increasing interest in health, and a suggestion, here and there, that the undergraduate medical curriculum need not be a stereotyped performance with a main utilitarian aim. Education is not synonymous with training: I hope it is ever true that our students might obtain education; we can safely reserve the term training for greyhounds. The suggestion that education in the Medical Faculty may have moved somewhat towards a technological training is something which should pull us all up with some quick thinking. The idea is abhorrent and would certainly have alarmed Sir Thomas Browne who, in 1643, regarded "human material" with reverence:

> "Thus we are men and we know not how; there is something in us that can be without us and will be after us, though it is strange that it hath no history what it was before us, nor can tell how it entered us . . . it is better to sit down in a modest ignorance, and rest contented with the natural blessing of our own reasons than buy the uncertain knowledge of this life, with sweat and vexation".

One of the greatest values of University life is the freedom of access of minds: but even in the days of the student-apprentice the same stood. Thomas Sydenham (c.1675) believed "the designs to attain to the right understanding of any Art or Profession included the choosing of some Eminent Men of the Art to be the guides and to provide Pattern and by whose Direction and Example, joyned with a tolerable Capacity . . . is the best and readiest way". It was not entirely incompatible with good progress that:

> In the days of Abernethy and Cheselden and Pott
> The dutiful apprentice had a very trying lot;
> He rose at five, and washed and dried the bottles on the shelf,
> He rolled the pills and bandages and then he washed himself,
> And after years of toil and sweat and a minimum of "brass"
> One famous day he was allowed to hold a cupping glass.

Good medical education should include a spirited interest in education in health or, more formally stated, "Health Education". Faustus in his more philosophic moments considered "the end of physic is our body's health"—but in a contrary phase of boastful revelry he overstated the curative aim:

> Couldst thou make men to live eternally,
> Or, being dead, raise them to life again
> Then this profession were to be esteem'd!

Our students should come to recognise that the public can have no greater asset than a close and continued relationship with a wise, sound, general medical adviser.

It is probably fortunate that most systems of education are constantly under the fire of general criticism: medical education, however, is unlikely to suffer from much stagnation, for, whenever the lay public stops criticising the type of modern doctor, the medical profession itself may be counted on to stir up the stagnant pool and cleanse it of its sedimentary deposit. It is hoped that the suggestion that students have been taught a great deal about the mechanism of disease but very little about the practice of medicine—that they are too much "scientific" and do not know how to take care of patients and people—will be firmly refuted. The vital importance of the personal relationship between physician and patient in the practice of medicine must form the background to most other considerations: the student should be encouraged in the thought that the profession should allow of intellectual freedom, give character as much chance as cleverness and yet be subject to the "tonic of difficulty and the spice of danger".

Teachers vary—some can think but have neither tongue nor technique; some are phonographic; some have technique but neither talk nor think; and some can think, talk and work. Be that as it may, the fact remains that some of the best instructors for students may have little conception of the highest lines of work, but have an immaculate ability to convey meaningful generalities. The greatest intellectual excitement comes from teachers with first-class minds who are talking about the fundamentals of the subject. Sir William Osler considered that a man may be a good student who reads only the book of nature.

Medical Education was called by a cynic "that most boring subject", but we, as teachers, violently reject the suggestion. In fact, after reading the "Foreword" by the Vice-Chancellor and "Some Thoughts of Medical Education" in this Journal (January, 1958), we have every reason to look forward to a thorough re-awakening of the joys and betterment of the medical student's task: to hope that there may be more time for self selection of studies and that the natural rule of elective attendance will be re-established (as was the common practice throughout the whole of the "final" year 25 years ago). The students can thus, so to speak, become "free swimmers". Each student will find his own way around and about the numerous facilities available to him. In fact, by such private enterprise, he will certainly discover a real University education: something which will lead on to a satisfying maturity in his pre-registration year and ultimately to that ever-widening conception of what a doctor should be—a teacher himself, aware of humanity in its widest senses; knowledgeable that Medicine is but a part of Nature's plan, that wide fields of enquiry into the aspects of Mental, Social, and Environmental health are awaited, and last, but not least, that success often turns on the snapping up of unconsidered trifles, even in the clinical world.

Medical Education will, we hope, fall into the general ideas (as expressed by the Royal College of Physicians) of a compromise between education in its true sense—the development of habits of learning and thought and an understanding of principles—on the one hand, and the acquisition of necessary technical knowledge on the other.

Yours sincerely,

A. V. NEALE.

Notes and News

Mr. R. V. Cooke has been elected President of the Section of Surgery of the Royal Society of Medicine.

Dr. G. Walters has been appointed whole-time consultant pathologist to the Wolverhampton group of hospitals.

M.R.C.P.: P. C. Farrant, M.B. (Brist.).

Crosby Leonard Price: R. C. Hodge.

Mackie Pathology Prize: R. T. Marcus and J. M. Slater (jointly).

Aberdeen Graduates Reunion. Will Aberdeen graduates in this region please send their names and addresses to Professor G. Lennon, University of Bristol.

NOTICE

LECTURE-DEMONSTRATIONS FOR GENERAL PRACTITIONERS

Sunday Mornings at 10.30 a.m.

13th Apr.: Department of Medicine, Bristol Royal Infirmary, **"Virus Diseases"**, J. MaCrae, M.D., CH.B., F.R.E.P.S., D.P.H.

20th. Apr.: Department of Medicine, Bristol Royal Infirmary, **"Certification of Unfitness for work"**, I. E. Phelps, M.R.C.S., L.R.C.P., D.C.H.

27th Apr.,: Department of Medicine, Bristol Royal Infirmary, **"Backache"**, K. H. Pridie, M.B., C.H.B., B.S., F.R.C.S.

4th May: Department of Medicine, Bristol Royal Infirmary, **"Iatrogenic Diseases"**, Professor C. Bruce Perry.

11th May: Department of Medicine, Bristol Royal Infirmary, **"Selection of Ulcer patients for Surgery"**, T. H. Butler, M.B., CH.B., F.R.C.S. and J. M. Naish, M.A., M.D., B.CHIR., F.R.C.P.

18th May: Bristol Eye Hospital, **"Demonstration of Normal and Abnormal Fundi"**, Anthony Palin, M.A., M.B., B.CHIR, F.R.C.S.E.

25th May: Whit Sunday—No Lecture.

1st June: Barrow Hospital, Barrow Gurney, **"Addicts and Psychopaths"**, R. E. Hemphill, M.A., M.D., B.A.O., D.P.M.

8th June: Department of Medicine, Bristol Royal Infirmary, **"Epilepsies"**, A. M. G. Campbell, D.M., F.R.C.P.

15th June: Bristol Maternity Hospital, **"Maternal Mortality, part ii"**, H. L. Shepherd, M.B., CH.M., F.R.C.O.G.

Applications to attend should be made to the Medical Postgraduate Dean, University of Bristol.

Appointments

UNITED BRISTOL HOSPITALS

December 1957—February 1958

Name	*Appointment*	*Formerly*
NICOL, W. A., L.D.S., R.F.P.S. (GLASGOW), D.D.O., (GLASGOW), DIPLOMA IN ORTHODONTICS (R.C.S.).	Consultant Orthodontist.	Assistant Orthodontist, Bristol Dental Hospital.
PHILLIPS, C. I., F.R.C.S., M.D. (ABERDEEN), D.O., R.C.S., P., ENG.	Consultant Opthalmic Surgeon.	Senior Registrar, St. Thomas's Hospital.
HORTON, R. E., M.B.E., M.S. (LONDON), F.R.C.S. (ENG.)	Consultant Surgeon.	Lecturer in Surgery, Bristol University. Hon. Assistant Surgeon, United Bristol Hospitals.
PANIKKAR, MISS T., M.B., B.S., D.A.	Registrar in Anaesthetics.	S.H.O. in Anaesthetics, Hitchin, Herts.
	BRISTOL	
SEAR, A. J., L.D.S., B.D.S. (B'HAM.)	Registrar to the Maxillo-Facial Unit at Frenchay Hospital and in the University of Bristol Dental Hospital.	Dental Officer, Public Health Department, City of Norwich.
BANNERMAN, H., M.B., B.S. (DURHAM), D.O.M.S.	Ophthalmologist, Bristol Clinical Area (School Clinics).	Recently (1957), Temporary Senior Registrar, Oxford Eye Hospital.
COULSTING, H.S., M.B., CH.B. (MANCHESTER), D.P.M. (MANCHESTER).	Consultant Psychiatrist (Child Guidance), Bristol Clinical Area.	Medical Director of Child Guidance Services to Cheltenham, Gloucester and County Child Guidance Service.
SEAGER, C. P., B.SC. (WALES), M.B., B.CH. (WALES), D.P.M. (LONDON).	Assistant Psychiatrist, Bristol Mental Hospitals Group.	Senior Registrar, Bristol Mental Hospitals.
COOPER, A. B., M.B., CH.B. (MANCHESTER), D.P.M. (CONJOINT BOARD).	Senior Registrar, Bristol Mental Hospitals.	Psychiatric Registrar, St. John's Hospital, Stone, Nr. Aylesbury, Bucks.
NEWSAM, P. N., M.B., B.CH. B.A.O. (BELFAST), D.P.H. D.M.R.D.	Senior Registrar in Radiodiagnosis, Southmead Hospital, Bristol.	Registrar in Radiodiagnosis, Royal Victoria Hospital, Belfast.
	NORTH GLOUCESTERSHIRE	
SHILLITO, P. W., M.R.C.S., L.R.C.P.	General Practioner Anaesthetist, Stroud General Hospital (2 sessions).	Is in general practice in Stroud.
LEITCH, D. S., M.B., B.S. (SYDNEY).	Surgical Registrar, Cheltenham General Hospital.	S.H.O. Birmingham Accident Hospital.
MESSENT, D. O. H., M.B., B.S. (SYDNEY).	Surgical Registrar, Gloucestershire Royal Hospital, Gloucester.	Holding same post on locum tenens basis.
LEWIS, J.W., M.B., B.S. (LONDON), D. (OBST), R.C.O.G.	Clinical Assistant in Gynaecology, Stroud General Hospital (1 session).	Is in general practice in Nailsworth.

BATH

Name	*Appointment*	*Formerly*
FALLA, H. P. L., M.B., B.S. (LONDON), D.A. (ENGLAND), D. (OBST.) R.C.O.G.	Anaesthetic Registrar, Bath Group of Hospitals.	S.H.O. Anaesthetist, Bath Group of Hospitals.
O'FLYNN, B. P., M.B., B.S. B.A.O. (N.U.I.).	Registrar in Pathology, Bath Group of Hospitals.	Pathologist in charge Laboratory at B.M.H., Iserlohn, R.A.M.C.

DEVON AND CORNWALL

ANKLESARIA, R. P., M.B., B.S. (BOMBAY).	Anaesthetic Registrar, Royal Devon & Exeter Hospital, Exeter.	House Physician, Northampton General Hospital.
SIMPSON, J. H., M.A., M.D. (CANTAB), M.R.C.P. (LONDON).	Consultant Physician with an interest in Geriatrics, Exeter Clinical Area.	Assistant Physician in Geriatrics, Norfolk and Norwich Hospital.
EDDY, H. D., B.M., B.CH. (OXON).	Clinical Assistant in General Medicine, West Cornwall Clinical Area (5 sessions).	Is in general practice in Truro and also holds appointment as Clinical Assistant in Neurology (2 sessions).
LIDDLE, W. W. J., M.B., B.S. (QUEENSLAND), F.R.C.S. (EDINBURGH).	Surgical Registrar, Torbay Hospital, Torquay and Newton Abbot Hospital.	Locum tenens appointment at Edinburgh Royal Infirmary.
CHURCHWARD, S. L., M.B., B.S. (SYDNEY).	Surgical Registrar, Royal Cornwall Infirmary, Truro.	Surgical Registrar, Otley General Hospital, Yorks.
PHILLIPPS, W. O. S., M.B., CH.B. (OTAGO, N.Z.), F.R.C.S. (EDIN.).	Surgical Registrar, South Devon and East Cornwall Hospital, Plymouth.	Surgical Registrar, Queen Mary's Hospital for Children, Carshalton.
PIGGOT, J., M.B., B.CH., B.A.O. (BELFAST), F.R.C.S. (EDIN.).	Research Assistant in the Registrar grade at the Princess Elizabeth Orthopaedic Hospital, Exeter.	Registrar to the Orthopaedic Service, Exeter Clinical Area.
RAI, M. Y., M.B., B.S. (MADRAS), F.R.C.S. (EDIN. AND ENG.).	Registrar to the Orthopaedic Service, Exeter Clinical Area.	S.H.O. in Orthopaedics, Royal Cornwall Infirmary, Truro.